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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/734,628	Applicant(s) CHINNAIYAN ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *1-50 and 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-59 and 61-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-69 are pending.

2. Applicant's election with traverse of Group XI, claims 51-59 (now claims 51-59 and 61-69) drawn to a method of *in situ* and *in vivo* imaging comprising a chimeric molecule which comprising RGD motif-comprising polypeptide of SEQ ID NO:1 and chemiluminescent polypeptide as the species, filed on 5-16-02, is acknowledged.

Applicant's traveral is on the grounds that a search directed to any of Groups I, XI and XVI would encompass a search for chimeric molecules comprising an RGD molecule and it would not be an undue burden for the Patent Office. Applicants also provide the same argument for rejoining Groups II, XII and XVII, Groups III, XIII and XVIII and Groups IV, V, XIV, XIX and XX. This is not found persuasive because Groups I-V, Groups XI-XIII and Groups XVI-XX are classified in different Classes and are recognized divergent subject matter. Specifically, the chimeric polypeptide molecule of Group I recites SEQ ID NO: 1 while the method of *in situ* and *in vivo* imaging Group XI recites a pharmaceutical formulation of SEQ ID NO:1 including method steps and the method of screening Group XVI recites different method steps. The methods and composition recited, therefore, in the restriction between Groups I and XI and XVI is proper. Therefore the methods and composition recited are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and separate classification of each Group.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-50 and 60 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 51-59 and 61-69 are under examination as they read a method of *in situ* and *in vivo* imaging comprising a chimeric molecule which comprising RGD motif-comprising polypeptide of SEQ ID NO:1 and chemiluminescent polypeptide as the species.

5. The disclosure is objected to because the "→" in page 26, line 24 is improper. Correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 51-59, and 61-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration of a pharmaceutical formulation which comprises a composition comprising a chimeric molecule wherein the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 and the image is generated by computer assisted bioluminescent imaging (BLI) does not reasonably provide enablement for a method *in situ* or *in vivo* imaging of any cell, any tissue any organ or a full body comprising administration of any pharmaceutical formulation in an amount sufficient to enhance the image, wherein the pharmaceutical formulation comprises any composition comprising any chimeric molecule and any pharmaceutically acceptable excipient as recited in claims 51, 52(a) 61, 62(a), 64 and 65(a), providing any imaging device as recited in claims 52(b), 62(b) and 65(b), administering the pharmaceutical formulation in an amount sufficient to generate the cell, tissue or body image as recited in claims 52(c), 62(c), and 65(c) and imaging the distribution of the pharmaceutical formulation with the imaging device, thereby imaging the cell, tissue or body as recited in claims 52(d), 62(d)and 65 (d); the method further comprising providing any substrate in claim 57; or a method for *in vivo* imaging a tumor neovasculature in any individual comprising the following steps: providing any pharmaceutical formulation comprising any chimeric molecule and any pharmaceutically acceptable excipient as recited in claims 59(a), 63(a), and 66(a) providing any imaging device as recited in claims 59(b), 63(b) and 66(b). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

Besides a chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 for *in situ* or *in vivo* imaging of a tumor neovasculature, the specification fails to provide any guidance as to how to make and how to use any "chimeric molecule" for *in situ* or *in vivo* imaging of a cell, a tissue, an organ or a full body.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient

working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant has not provided sufficient biochemical information that distinctly identifies such "chimeric molecule" other than the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1. While any "RGD motif-comprising polypeptide" may have some notion of " integrin recognition", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification (page 15, lines 10-25) fails to provide any guidance on how to make RGD motif-comprising polypeptide, any chimeric molecule, any pharmaceutical formulation, any imaging device can be used for *in situ* or *in vivo* imaging a tumor neovasculature in an individual.

The term "Comprises" in claims 67-69 is open-ended, it expand the amino acid sequence of SEQ ID NO:1 to include additional non disclosed amino acids outside of the "RGD motif-comprising polypeptide". There is insufficient guidance as to which amino acid segments within the polypeptide can be unique and retain a distinct functional capability of "RGD motif-comprising polypeptide". Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid fragment can retain the functional capabilities of the RGD motif-comprising polypeptide requires knowledge of, and guidance with regard to, which segments in the polypeptide's sequence contribute to its function.

Minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Therefore, structurally unrelated compounds comprising any "RGD motif-comprising polypeptide" would be expected to have greater differences in their activities. Further, RGD-motif-comprising polypeptide is the primary site of recognition by integrins that are expressed on tumor cells and are responsible for tumor invasion. Therefore, there is insufficient direction and guidance as how the method for *in situ* or *in vivo* imaging of any cell, any tissue, any organ or any full body will be accomplished with the RGD-motif-comprising polypeptide.

Therefore, there is insufficient direction or objective evidence as to how to make and to how to use any chimeric molecule comprising RGD motif-comprising polypeptide which can be used for in *situ* or in *vivo* imaging of tumor neovasculature for the number of possibilities associated with the myriad of direct and indirect effects associated with

various "chimeric molecule" and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 51-59, and 61-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration of a pharmaceutical formulation which comprises a composition comprising a chimeric molecule wherein the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 and the image is generated by computer assisted bioluminescent imaging (BLI, however applicant is not in possession of a method *in situ* or *in vivo* imaging of any cell, any tissue any organ or a full body comprising administration of any pharmaceutical formulation in an amount sufficient to enhance the image, wherein the pharmaceutical formulation comprises any composition comprising any chimeric molecule and any pharmaceutically acceptable excipient as recited in claims 51, 52(a) 61, 62(a), 64 and 65(a), providing any imaging device as recited in claims 52(b), 62(b) and 65(b), administering the pharmaceutical formulation in an amount sufficient to generate the cell, tissue or body image as recited in claims 52(c), 62(c), and 65(c) and imaging the distribution of the pharmaceutical formulation with the imaging device, thereby imaging the cell, tissue or body as recited in claims 52(d), 62(d)and 65 (d); the method further comprising providing any substrate in claim 57; or a method for *in vivo* imaging a tumor neovasculature in any individual comprising the following steps: providing any pharmaceutical formulation comprising any chimeric molecule and any pharmaceutically acceptable excipient as recited in claims 59(a), 63(a), and 66(a) providing any imaging device as recited in claims 59(b), 63(b) and 66(b).

Applicant has disclosed only a chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1; therefore, the skilled artisan cannot envision all the contemplated chimeric molecule possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a

claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 51-59 and 61-69 are rejected under 35 U.S.C. 103(a) as being obvious over U.S Patent No. 5,650,135 (IDS reference AB), in view of U.S Patent No. 6,087,476 (IDS reference AA) and further in view of U.S Patent No. 6,180,084.

The '135 patent teaches methods and compositions relating to non-invasive imaging and/or detecting of light-emitting conjugates in mammalian subjects (*in vivo*). The conjugates contain a biocompatible entity and a light-generating moiety. Biocompatible entities include, but are not limited to, small molecules; macromolecules; microorganisms; eukaryotic cells; all types of pathogens and pathogenic substances; and particles (column 7, lines 13-21 in particular). Light-generating moieties are typically molecules or macromolecules that give off light. They may generate light as a result of radiation absorption (e.g. fluorescent or phosphorescent molecules), or as a result of a chemical reaction (e.g. bioluminescent proteins). Exemplary light-generating moieties are bioluminescent proteins, such as luciferase and aequorin (column 2 lines 63-67 and column 3 lines 1-5 in particular). Luciferases require a substrate, such as luciferin (column 10, lines 33-35 in particular). The method includes administering to the subject a conjugate of the entity and a light-generating moiety (column 2, lines 63-64 in particular). In addition, the '135 patent teaches that a conjugate can be administered intravenously (column 15, lines 23-24 in particular) and images were taken at 24 hours post inoculation, the bioluminescent signal is localized at a single focus in all infected animals (see FIGS. 5A, 5C and 5E in particular).

The '135 further teaches that animals or objects to be imaged were immobilized in a light-tight box containing a door and a charge-coupled device (CCD) camera with a two stage microchannel intensifier head. The camera was attached, via cables leading out of the box, to an image processor (column 26, lines 43-49 in partuclar). The image processors are usually connected to a personal computer. Once the images are in the form of digital files, they can be manipulated by a variety of image processing programs and printed (column 17, lines 6-13 in particular).

The claimed invention differs from the reference teachings only by the recitation that the chimeric molecule comprising a first domain comprising a bioluminescent and a second domain comprising an RGD motif-comprising polypeptide.

The '084 patent teaches a tumor homing molecule is linked to a moiety that is detectable external to the subject, thereby providing a composition useful to perform an in vivo diagnostic imaging study. For example, in vivo imaging using a detectable labeled tumor homing peptide can identify the presence of a tumor in a subject (column 37, lines 4-9 in particular). A tumor homing molecule binds specifically to a sample of the tumor obtained from the patient. For example, the RGD-4C (CDCRGDCFC; claimed and reference SEQ ID NO:1) binds to blood vessels in microscopic sections of human tumors, whereas little or no binding occurs in the blood vessels of non-tumor tissues (column 25, lines 46-52 in particular). Furthermore, tumor homing molecules can bind to the endothelial lining of small blood vessels of tumors. The vasculature within tumors is distinct, presumably due to the continual neovascularization, resulting in the formation of new blood vessels required for tumor growth. The distinct properties of the angiogenic

neovasculature within tumors are reflected in the presence of specific markers in endothelial cells and pericytes (column 35, lines 44-50 in particular).

The `476 patent teaches chimeric proteins obtained by genetic engineering. Such chimeric proteins comprise a continuous polypeptide sequence in which a photoprotein is linked to an antigenically active protein or fraction thereof. The `476 patent further teaches that chimeric proteins which comprise a continuous polypeptide sequence in which a photoprotein is linked to a protein with specific affinities for analytes of interest and methods of using these proteins in immunodiagnostic or imaging processes (column 1, lines 15-28 in particular). The chimeric protein constructed as a continuous polypeptide sequence and comprised of a photoprotein and a second protein. The photoprotein is a protein having luminescent properties and is typically chosen from a class of compounds known as luciferases. Finally, the `476 patent teaches that the chimeric proteins can be used to detect antibodies, antigens, or other specifically binding proteins.

Claim 56 is included because the claimed time between about 2 minutes and 24 hours is within the `135 patent reference time, that is 24 hours.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to link the RGD containing peptide (claimed SEQ ID NO:1) taught by `084 patent with the photoprotein with luminescent properties taught by the `476 patent and use the resultant chimeric molecule in the methods of imaging taught by the `135 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the tumor homing RGD-containing peptide binds specifically to a sample of the tumor obtained from the patient taught by `476 patent and the resultant chimeric protein can be used to detect specific binding proteins taught by `476 which reflect in the presence of specific markers in endothelial cells taught by the `084 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

12. **1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
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July 15, 2002

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